REMARKS

Claims 1-65 and 70-74 are pending and under examination. Claims 66-69 are withdrawn from consideration as being directed to a non-elected invention. Applicants reserve the right to pursue these claims in a later filed application claiming the benefit of the subject application. By the present communication, claims 1, 18, 19, 21 and 34 have been amended. Support for the amendments can be found throughout the application as filed. In particular, support for the amendments can be found at, for example, paragraphs [0042]-[0043]. Claims 18, 19 and 21 have been amended to correct an obvious informality and now depend from claim 1. Accordingly, the amendments do not raise an issue of new matter. Applicants have reviewed the Office Action mailed February 26, 2007, and respectfully traverse all grounds of rejection for the reasons that follow.

Applicants acknowledge that priority of claims 1-74 has been accorded to provisional application serial numbers 60/272,754, filed March 1, 2001. Applicants further acknowledge the withdrawal of various grounds of rejection under 35 U.S.C. §112, first and second paragraphs, and the withdrawal of the §101 rejection with respect to claims 71-74.

Rejections under 35 U.S.C. §101

Applicants respectfully traverse the rejection of claims 1-16, 23-65 and 70 under 35 U.S.C. §101 as allegedly being directed to non-statutory subject matter. Specifically, the Office maintains that claims 1-16 and 23-33 consist of non-functional descriptive data or that claims 1-16, 23-65 and 70 do not produce a tangible result.

Without acquiescing to the reasoning offered by the Office, and in order to expedite prosecution of the instant application, Applicants have amended claim 1 to recite a computer readable medium or media having stored thereon computer-implemented instructions causing a processor to perform the steps of providing both a data structure relating a plurality of reactants to reactions of a biochemical network and a constraint set and determining at least one flux distribution wherein the flux distribution determines a systemic property that is dependent upon a regulated reaction. Claim 34, directed to a method for determining a systemic property of a

biochemical reaction network, has been amended to recite that the output provided to a user is a separate step. Therefore, the claims clearly recite both a physical transformation since the claimed computer-implemented instructions cause a processor to perform steps for determining a systemic property and since an output is provided to a user as well as a useful, concrete and tangible result since the output provides the identification of a systemic property of a biochemical reaction network. In light of these amendments, Applicants respectfully submit that the claims produce a tangible result, and request withdrawal of the rejection.

Rejections under 35 U.S.C. § 112, Second Paragraph

Applicants respectfully traverse the rejection of claims 18-22 under 35 U.S.C. §112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Office Action alleges that claims 18-22 are dependent from canceled claimed 17, and are therefore not complete. Without acquiescing to the reasoning offered by the Office, and in order to expedite prosecution of the instant application, Applicants have amended claims 18, 19 and 21 to depend from claim 1. Accordingly, withdrawal of the rejection is respectfully requested.

Applicants respectfully traverse the rejection of claims 34-65 and 70 under 35 U.S.C. §112, second paragraph, as allegedly being incomplete for omitting essential elements. Specifically, the Office Action alleges that no where in claim 34 does applicant disclose how a user is to be provided with the necessary information. Without acquiescing to the reasoning offered by the Office, and in order to expedite prosecution of the instant application, Applicants have amended 34 to remove the term "thereby" and include the phrase "providing said systemic property of said biochemical reaction network to a user" as a separate step. Accordingly, withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. § 102

Applicants respectfully traverse the rejection of claims 1-2, 5-7, 23-26, 29, 32, 34, 40, 53-54, 56-61 and 64-66 under 35 U.S.C. §102(a) and under 35 U.S.C. §102(e) as allegedly

anticipated by WO 00/46405 to Palsson. Specifically, the Office alleges that the purported constraints described in WO 00/46405 fall within the meaning of the terms variable and function as claimed by the invention.

Applicants respectfully submit that WO 00/46405 is not applicable art under §102(e) because it is an international application that does not list the United States as a designation.

With respect to the §102(a) rejection, Applicants submit that the Office has failed to establish a *prima facie* case of anticipation because WO 00/46405 fails to teach a regulated reaction as claimed. A regulatory reaction refers to first and second reactions related by a function that alters the flux through the second reaction dependant on a condition. That condition is the result of the first reaction (see, for example, paragraphs [0032] and [0033] of the specification as filed.).

The constraints described by WO 00/46405 are distinguishable from the claimed regulated reaction because they are not acted on by a function that relates a first and second reaction and changes the value of the second reaction. The value of the constraints described by WO 00/46405 is not dependent on a condition during determination of a systemic property. As set forth in Applicants previous response, the constraints referred to in WO 00/46405 correspond to a set of limits to linear equations. The limits described therein are not variable and are not acted upon by a function that relates a first reaction to a second reaction. Moreover, the instant application expressly distinguishes WO 00/46405 when it describes that the constraint-based modeling described therein defines a solution space, and that the incorporation of a regulated reaction as claimed reduces the dimensionality and volume of the solution space to improve predictive capabilities (see, for example, paragraphs [0023]-[0026] of the specification as filed). Accordingly, Applicants respectfully submit that the claimed regulated reaction is distinct from the constraints described in WO 00/46405, and respectfully request withdrawal of the rejection.

Rejections Under 35 U.S.C. § 103

Applicants respectfully traverse the rejection of claims 1-7, 9, 14-15, 23-24, 39-40, 42-45, 48-49, 51-61, 64-65 and 70-74 under 35 U.S.C. §103(a) as allegedly being obvious over Blanch et al., in view of Alberty. Specifically, the Office Action alleges that Blanch et al.

describe the mechanism of chymotrypsin, showing multiple reactions, stoichiometric coefficients, substrates, products and an allegedly reversible reaction. The Action further alleges that partial derivatives of enzyme-substrate concentrations are variable constraints equated with a function whose value is zero, and that such constraints are boundary constraints that are regulators of the flux distributions because they minimize an objective function, corresponding to the partial derivatives of complex concentration with respect to time, to a steady state condition.

The Action relies upon Alberty for allegedly describing matrices with stoichiometric coefficients and binary variables for a system of 21 reactions and 30 reactants, which is solved using linear equations wherein a variable constraint on the system is the pH value because it affects the proton balance. The Action concludes that it would have been obvious to modify the chymotrypsin model of Blanch et al. by use of the computerized linear analysis methods of Alberty because Blanch et al. allegedly describes the claimed method, and Alberty extends this method to computer systems for linear optimization.

The recent U.S. Supreme Court decision in the KSR International v. Teleflex Inc. (82 USPQ2d 1385), modified the standard for establishing a *prima facie* case of obviousness. Under the KSR rule, three basic criteria are considered. First, some suggestion or motivation to modify a reference or to combine the teachings of multiple references still has to be shown. Second, the combination has to suggest a reasonable expectation of success. Third, the prior art reference or combination has to teach or suggest all of the recited claim limitations. Factors such as the general state of the art and common sense may be considered when determining the feasibility of modifying and/or combining references.

Applicants respectfully point out that independent claim 34 is not subject to a rejection under 35 U.S.C. §103(a). Further, claims 39-40, 42-45, 48-49, 51-61, 64-65 and 70 depend from claim 34, and therefore, contain all of the elements of base claim 34. Since claim 34 been deemed to be unobvious over the cited combination of references, any dependant claims must also be unobvious. Accordingly, Applicants respectfully submit that the rejection is moot with respect to claims 39-40, 42-45, 48-49, 51-61, 64-65 and 70, and request its withdrawal.

With respect to claims 1-7, 9, 14-15, 23-24 and 71-74, the cited combination of references fails to establish a *prima facie* case of obviousness because Blanch et al. and Alberty do not teach or suggest a regulated reaction as claimed. Independent claims 1 and 71 recite a data structure having a regulated reaction. The application teaches that a regulated reaction experiences an alteration when it describes:

> [T]he term "regulated," when used in reference to a reaction in a data structure, is intended to mean a reaction that experiences an altered flux due to a change in the value of a constraint or reaction that has a variable constraint.

Paragraph [0032] (emphasis added) (*see also* paragraph [0033] describing that the change is due a first reaction that alters a variable constraint of the second reaction).

The combination of Blanch et al. and Alberty fails to teach or suggest a reaction that experiences an altered flux due to a change in the value of the constraint of a different reaction. As such, the recitation of the steady-state Michaelis-Menten reaction rate in Blanch et al. fails to teach or suggest a reaction experiencing an altered flux due to a change exerted on it by another reaction because the reaction is at steady-state, and by the Examiner's apparent admission, the alleged variable constraints are equated to zero. A value equated to zero does not experience an altered flux due to a change in its value. Similarly, the characterization of such constraints, being boundary constraints that are regulators, is non-analogous because there is no alteration in the value of these constraints based on a first, different reaction nor do they minimize or maximize an objective function as this term is understood to mean in the computer or mathematical arts.

The Office's assertion that such steady-state equations of Blanch et al. are solved with respect to variable constraints corresponding to different time points, or that the pH values of Alberty correspond to variable constraints, also fails to teach or suggest the claimed regulated reaction because these items similarly do not experience an alteration in their value based on a first reaction. For each alleged time point, the time value of that point is constant for the alleged calculation. Similarly, the method of Alberty calculates a solution at a specified pH value. Moreover, the instant application expressly teaches that the claimed methods provide improved predictive capabilities over methods such as those described in Alberty when it describes:

> A solution space is defined by constraints such as the well-known stoichiometry of metabolic reactions as well as reaction thermodynamics and capacity constraints associated with maximum fluxes though reactions. These are examples of physical-chemical constraints that all systems must abide by.
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> ****
>
> [T]his solution space describes the functional capabilities of the organism as described for example in WO 00/46405. . . . These and other constraints-based models known in the art can be modified according to the methods of the present invention in order to produce models capable of predicting the effects of regulation on systemic properties or to predict holistic functions of these organisms.
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> ****
>
> As useful as the defined solution spaces resulting from stand-alone constraints-based models are for conceptual and basic scientific purposes, they have limited predictive ability, due to their large volume and dimensionality. The present invention provides methods to incorporate constraints that are associated with how the functional operation of reaction networks are controlled/regulated. An advantage of the invention is that the dimensionality and volume of the solution spaces can be reduced due to the incorporation of regulatory constraints into a constraints-based model, thereby improving the predictive capabilities of the model.

Paragraphs [0023]-[0026] (emphasis added).

Since Blanch et al. and Alberty fail to describe a reaction that experiences an altered flux due to a first reaction, and since the methods of Alberty have limited predictive abilities compared to the claimed regulatory reactions, the cited combination of references cannot render the claimed invention obvious. Applicants therefore respectfully request withdrawal of this ground of rejection.

Applicants respectfully traverse the rejection of claims 1, 8, 10-13, 34, 41 and 46-47 under 35 U.S.C. §103(a) as allegedly being obvious over Blanch et al. in view of Alberty and further in view of Grewal et al. Applicants respectfully submit that the arguments provided above apply equally and are incorporated here. The Office Action relies upon Grewal et al. for allegedly describing computer modeling of a receptor-ligand interaction. The Action concludes that it would have been obvious to modify the method of Blanch et al. and Alberty with Grewal

et al. because Grewal et al. allegedly has the advantage of teaching signal transduction and receptor-ligand interactions.

Applicants respectfully submit that Grewal et al. is absolutely silent with respect to inclusion in any reaction data structure, a regulated reaction as described and claimed. Since Blanch et al., Alberty and Grewal et al. all fail to teach or suggest a regulated reaction that experiences an altered flux due to a change in the value of its constraint based on a different reaction, the cited combination cannot render the invention as claimed obvious. Therefore, Applicants respectfully request withdrawal of this ground of rejection.

Applicants respectfully traverse the rejection of claims 1-16 and 23-33 under 35 U.S.C. §103(a) as allegedly being obvious over Edwards et al. The Office Action alleges that Edwards et al. differs from the claimed invention only by the computer content on the claimed computer readable media. Asserting that the claims are directed to nonfunctional descriptive material, the Action alleges that the claims are not entitled to patentable weight. Without acquiescing to the reasoning offered by the Office, and in order to expedite prosecution of the instant application, Applicants have amended claim 1 to recite computer-implemented instructions that cause a processor to perform recited functions. Therefore, the assertion that the claims are directed to nonfunctional descriptive material is moot.

Applicants respectfully submit that Edwards et al. describes the solution space method, as described above, which lacks the predictive capabilities of the claimed invention incorporating regulated reactions. Absent some teaching or suggestion of a regulated reaction as required by the claimed invention, Edwards et al. cannot render the invention obvious. Accordingly, withdrawal of this ground of rejection is respectfully requested.

CONCLUSION

In summary, for the reasons set forth herein, Applicants submit that the claims are in condition for allowance and respectfully request a notice to this effect. If the Examiner would like to discuss any of the issues raised in the Office Action, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

The Commissioner is hereby authorized to charge $510.00 as payment for the Petition for Three-Month Extension of Time fee ($510.00) to Deposit Account No. 07-1896. Additionally, the Commissioner is hereby authorized to charge any other fees that may be due in connection with the filing of this paper, or credit any overpayment to Deposit Account No. 07-1896.

Respectfully submitted,

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